December 14, 2004

John F. Murray, CAE
Executive Director
Biphenyl Work Group (BWG)
1850 M Street, N.W.
Suite 700
Washington, DC 20036

Dear Mr. Murray:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Biphenyl posted on the ChemRTK HPV Challenge Program Web site on February 18, 2004. I commend the Biphenyl Work Group for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Workgroup advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Don Rodier, Acting Chief of the HPV Chemicals Branch, at 202-564-7633. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Biphenyl

SUMMARY OF EPA COMMENTS

The sponsor, The SOCMA Biphenyl Working Group, submitted a test plan and robust summaries to EPA for Biphenyl, CAS No. 92-53-4, dated December 29, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 18, 2004.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

2. Environmental Fate. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

3. Health Effects. Adequate data are available for the acute, repeated-dose, reproductive and developmental toxicity, and gene mutation endpoints for the purposes of the HPV Challenge Program. The submitted data for chromosomal aberrations are inadequate for the purposes of the HPV Challenge Program. Unless the submitter can provide robust summaries for additional studies to support a weight-of-evidence approach, an *in vitro* test following OECD TG 473 is needed to address this endpoint. The submitter also needs to address deficiencies in the robust summaries.

4. Ecological Effects. The submitted toxicity data for the fish and invertebrate endpoints are adequate for the purposes of the HPV Challenge Program. Data for the algal endpoint are inadequate.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE BIPHENYL CHALLENGE SUBMISSION

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for these endpoints are adequate for the purposes of the the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for the acute, repeated-dose, reproductive and developmental toxicity, and gene mutation endpoints. The submitter needs to provide missing details in the robust summaries.

Genetic toxicity (chromosomal aberrations). EPA does not consider this endpoint to be adequately addressed by the submitted cytogenetic assay using Chinese hamster DON cells because of the following deficiencies cited by the submitter: (1) the absence of testing with a metabolic activation system, (2) uncertainty about whether the highest concentration was cytotoxic, (3) the lack of test concentrations above 1mM (OECD TG 473 recommends a high concentration of 10mM), and (4) the examination of an insufficient number (100) of metaphases (half the recommended number).

The submitter identified but did not provide robust summaries for several other chromosomal aberration studies, including one (Sofuni et al., 1985) in which positive results were observed with metabolic activation. EPA recommends that the submitter provide robust summaries for these studies if they can support a weight-of-evidence approach. If not, EPA recommends an *in vitro* test following OECD TG 473 to address this endpoint.

Ecological Effects (fish, invertebrates, and algae)

The submitted data for acute toxicity to fish and invertebrates are adequate for the purposes of the HPV Challenge Program.

Fish. In order to enhance the key fish study, the submitter needs to provide adequate robust summaries for other acute fish toxicity tests mentioned in the test plan (see p. 9).

Algae. Data for this endpoint are inadequate. The 3-hour study duration of both submitted studies fell short of the 72-hour or 96-hour duration recommended by OECD 201. Testing is needed using measured concentrations.

Specific Comments on the Robust Summaries

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

For those studies summarized from information in the CICAD documents, revised robust summaries need to be based on the primary reference study reports.

Acute toxicity. The robust summary for the acute oral toxicity study in male and female Sprague-Dawley rats (Monsanto Project No. Y-76-263, 1976) is missing details, including test substance purity, age of the animals, method of dose administration, control group data, and statistical analysis and standard deviation.

Repeated-dose toxicity. The robust summary for the 750-day study (Ambrose et al., 1960) is missing details, including test substance purity, statistical methods and statistical significance of results. There is also an error in recording the highest dose tested in the robust summary.

The robust summaries for the two 104-week bioassays in rats and mice (JBRC, 1996) are missing details, including the test guideline or standardized test method used, test substance purity, complete lists of organs and tissues weighed and histologically examined, statistical methods and statistical results.

Genetic toxicity. The robust summary for the bacterial reverse mutation assay is missing details, including test substance purity and GLP compliance.

Reproductive toxicity. The robust summary for the three-generation study in Long-Evans male and female rats is missing details, including test substance purity, the test guidelines or standard methods used, GLP compliance, sex of the pups, number of live births and stillbirths, details on infertile animals, estrus cycle and sperm parameter data, complete list of male and female reproductive organs and tissues harvested, preserved and examined histopathologically, and statistical methods used.

The robust summary for the oral study in male and female rats of unspecified species (Ambrose et al., 1960) is missing details, including test substance purity, test guideline or standardized method used, GLP compliance, sex of pups, body weight data, number of live births and stillbirths, details on infertile aniimals, and statistical analyses of reproductive data. Test concentrations were also inconsistently reported in the summary.

In the robust summaries for the 2-year studies in male and female Fischer 344/DuCrj rats and Cjr:BDF 1 mice, the submitter speculates about the male and female reproductive organs that might have been examined. There is no explicit substantiation that any of the reproductive organs were weighed, or that a full range of reproductive organs (e.g., ovaries, testes, epididymides, and accessory sex organs) was examined histologically. In addition, the test concentrations reported in the robust summaries are not consistent with the concentrations reported in the cited secondary reference (CICAD No. 6, Biphenyl). Additonal information missing from one or both of the robust summaries includes test substance purity, test guideline or standard method used, GLP compliance, control groups and responses, complete list of organs examined and weighed, and the details of the statistical methods and analyses performed.

Developmental toxicity. The robust summary for the oral study in female Wistar rats is missing details on test substance purity and the test guideline or standardized method used. The robust summary for the oral study in female CLFP (ICI strain) outbred mice is missing details, including the test substance purity, data for developmental endpoints examined (e.g., number of corpora lutea, number and type of implantations, fetal body weight, and sex ratio), and the results of statistical analyses for some parameters.

Ecological Effects (fish, invertebrates, and algae)

The input parameters used for ECOSAR to derive toxicity values reported in the test plan for fish, invertebrates, and algae need to be reported in the robust summaries.

Fish. Missing study details include test guideline followed, purity of the test substance, and loading rate of the fish. Although two controls (vehicle and water only) were reportedly used, results were provided for only one control. It is unclear which control values are being reported.

Invertebrates. The test guideline followed and loading rate of the daphnids were not reported in the robust summary of the key study.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.